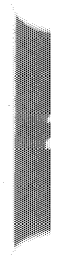

Introduction

This document provides information in support of the rule-making for the Topical Antimicrobial Drug Products for Over-the-Counter Human Use; Tentative Final Monograph for Health-Care Antiseptic Drug Products (TFM) 59 Fed. Reg. 31401 (June 17, 1994). Since 1994 the Soap and Detergent Association and the Cosmetic, Toiletry, and Fragrance Association (SDA/CTFA) Industry Coalition ("Industry Coalition") has made a number of submissions to FDA providing data and comment pertinent to monograph rule-making, including comments on the TFM and the proposal of the Healthcare Continuum Model (HCCM) (submitted June 13, 1995), a detailed proposal on finished product testing (submitted September 29, 1999), a Citizen Petition for proposed labeling for product categories in the HCCM (submitted April 2, 2001), a Citizen Petition addressing several OTC Monograph flexibility issues associated with the TFM (submitted June 1, 2001), and a Citizen Petition on healthcare products, product performance criteria, and active ingredients (submitted August 6, 2001).

The purpose of this petition is to provide the Agency with the specific information requested in November 1999 on testing, including time kill kinetic studies, and the results of a study on the effects of neutralization on surrogate endpoint testing. We are also providing a copy of the December 8, 1999 letter to the Agency confirming the agreements that were reached at that meeting, as well as a copy of the Industry Coalition Proposal for Finished Product Efficacy Testing of Health Care Antiseptic Drug Products September 29, 1999.

The following general principles serve as guidance for selecting and validating appropriate test methods:

- Standardized, defined, and peer-reviewed test methodologies ensure reliability, reproducibility and comparability of test results.

- Appropriate methods should simulate actual use conditions, present a minimum of hazard to investigator and subject, be reasonably economical, and be flexible enough to handle a variety of product forms.

- Antimicrobial test methods should use a reliable and readily available supply of standardized microorganisms.

- In situations where product form, ingredients, or other factors preclude the use of a method, use of an equivalent method should be allowed, provided it meets the general guidelines embodied in the original test method.

American Society for Testing and Materials (ASTM) methods are proposed for testing because they embody these principles. Use of ASTM procedures ensures that periodic, peer review of the methods will maintain their validity, currency, and reproducibility.

Consistent with an ingredient-based monograph approach, a regimen incorporating both *in vitro* and *in vivo* tests is proposed. This approach provides data on the speed of action of a finished product (*in vitro* test), and demonstrates its ability to meet the effectiveness criteria using the *in vivo* test noted for the proposed indication.

In vitro and *in vivo* surrogate end-point test methods demonstrate the potential efficacy of topical antibacterial products. *In vitro* time kill kinetic tests demonstrate the potential speed of antibacterial activity of the product against bacteria representative of the use situation(s). *In vivo* test methods demonstrate the product attributes under conditions that simulate use situation(s). The key performance attribute of a topical antimicrobial product is effectiveness against bacteria representative of those encountered in the targeted situation. Depending on the situation and task, fast action, persistence, and/or cumulative effect may also be desirable attributes.

Persistence is defined as the prolonged or extended antimicrobial activity that prevents or inhibits the proliferation or survival of microorganisms after application of the product. This may be demonstrated by sampling a site several minutes or hours after application and demonstrating bacterial antimicrobial effectiveness over a baseline.

Cumulative effect is defined as a progressive decrease in the numbers of microorganisms recovered following repeated applications of a test material. This manifests itself in *in vivo* surrogate end point tests as an increase in the $\log_{10}$ reductions of products following two or more applications. This effect should not be confused with persistence, which is time, rather than application dependent.

An active ingredient listed in an OTC monograph as effective and safe (Category I) has had the breadth of its efficacy attributes established during the formal drug review process including spectrum of activity. Therefore, when Category I active ingredients are used in topical antimicrobial product formulations, testing is needed only to confirm the effectiveness of the final formulation and to elucidate desired key attributes such as persistence, and speed of activity. Supplemental methods may be used to demonstrate attributes of the formula to support other truthful and not misleading statements, not necessarily indications or label claims.

Status of Methodology since 1999

In September 1999 the Industry Coalition submitted a briefing document (Vol. II) to the Agency detailing its position on many technical issues that need to be addressed to achieve test methodologies that are reliable, reproducible and able to allow comparison of test results. At the feedback meeting held November 3, 1999, the following agreements were reached:

- MIC testing of Category I active ingredients should not be part of the finished product efficacy testing requirements in the final rule making.
- Control of methodology is necessary to ensure validity.

The information in the following two sections (Tabs 6 and 7) addresses each of these points.